REMARKS

Claims 1-14 are pending. Claims 1-14 stand rejected. Claims 1, 5, 6, 7, 9, and 14 have been amended. Support for amended claims 1, 6, and 7 can be found in the specification and claims as originally filed. Support for amended claims 5 and 14 can be found for example on page 5 line 19 through page 6 line 2, Table 1 and Figure 1. Support for amended claim 9 can be found for example on page 7 lines 23-24. New claim 15 has been added. Support for new claim 15 can be found for example on page 5 lines 19-22.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Brief Summary

Applicant respectfully submits that it was the first to discover that a cephalotaxine, such as homoharringtonine, inhibits angiogenesis. None of the references cited by the Examiner teach or suggest this discovery. Reconsideration of the claims and a withdrawal of all rejections in light of the following remarks is requested.

Claim Objections

Claims 1, 6 and 7 are objected to because of informalities. Claim 6 has been amended to overcome the Examiner's objections.

The Examiner has asserted that "the objectives of 'treatment' (claim 1) and 'prophylactic' (claim 7) are inconsistent with the function of the amount of the cephalotaxine, i.e., 'in an

amount *to inhibit* . . . '" Page 2 of the Office Action. Applicant respectfully disagrees. The Examiner has not provided support for this assertion. The present invention provides methods of "treating an angiogenic disease in a host" (claim 1) and "prophylactically treating an angiogenic disease in a host" (claim 7). In each case, the claim requires "contacting said host with a cephalotaxine with an amount sufficient to inhibit." This requirement in both claims consistent as supported by the specification. For example, page 7 lines 11-12 of the specification provide that cephalotaxine may be "administered in an amount sufficient to inhibit angiogenesis thereby inhibiting progression of angiogenesis and the angiogenic disease." In addition, the specification also provides, for example, prophylactic treatment as the "administration of a cephalotaxine to a host to prevent the onset or progression of an angiogenic disease." Page 9 lines 13-14. Thus, the claim terms are consistent. Applicant respectfully requests the withdrawal of the objections to claims 1, 6, and 7.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner has stated that the specification fails to enable a method of prophylactic treatment or inhibition of the onset of the disclosed diseases/disorders. It has been argued by the Examiner that there is "reason to doubt the statements in the specification that angiogenic diseases can actually be prevented." In addition, the Examiner cites the rule set forth in *In re Marzocchi,* 169 USPQ 367, 370 (CCPA 1971), which states that a specification complies with the enablement requirement "unless there is reason to doubt the objective truth of statements" made therein. Here, the Examiner argues that

the "objective truth of the statement that an angiogenic disease could actually be prevented" is in doubt. In support of this position, the Examiner has relied on various references that disclose the lack of success in identifying cures and preventative measures for angiogenic diseases.

The Examiner's application of *In re Marzocchi* amounts to a rejection based on 35 U.S.C. § 101 according to M.P.E.P § 2107.02 III. A. However, M.P.E.P. § 2107.02 III. B. states

> Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

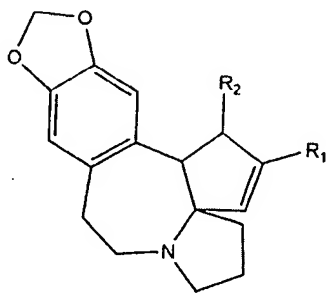
Thus, the Examiner's sole reliance on a "previous lack of success" in the cure or prevention of angiogenic diseases is an insufficient basis for maintaining a 35 U.S.C. § 101 rejection. As stated in M.P.E.P § 2107.01 IV., a "35 U.S.C. § 112, first paragraph rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. § 101." Therefore, the Examiner has no basis for maintaining the rejection under 35 U.S.C. § 112, first paragraph.

In addition, the specification is enabling for the present invention because it shows the anti-angiogenic effect of the compounds of the invention. Specifically, Table 2 in Example 1 summarizes the data from an experiment testing the effect of homoharringtonine upon angiogenesis in the chicken chorioallantoic membrane (CAM) (see pages 14-16 of the specification). The data demonstrates that the application of increasing amounts of a cephalotaxine shows a corresponding decrease in the length of the blood vessels in the CAM. Thus, the specification is enabling.

Applicant respectfully requests the withdrawal of this rejection.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 5, 9 and 14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner has stated that the term "analog" is indefinite. Claims 5 and 14 have been amended to recite "a compound of the formula



wherein R_1 is an ester or a substituted alkyl and wherein R_2 is an ester or a substituted alkyl.

The Examiner has stated that the term "micro" in claim 9 is indefinite. Claim 9 has been amended to recite "cancer cells that have not yet been vascularized to form a solid tumor." As currently amended, claims 5, 9, and 14 are definite and clear.

Applicant respectfully requests the withdrawal of the rejection of claims 5, 9, and 14 under 35 U.S.C. § 112, second paragraph.

Claim Rejection Under 35 U.S.C. § 103(a)

A. Powell in view of D'Amato and Kawai

Claims 1 and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powell et al. U.S. Patent No. 3,793,454 ("Powell") in view of D'Amato et al. U.S. Patent No.

5,712,291 ("D'Amato") and Kawai et al., *Cancer Lett.* 2001 Oct. 10; 171(2):201-07 ("Kawai"). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

1. The references fail to teach every limitation of claim 1 and those depending therefrom.

As currently amended, claim 1 recites a "method of treating an angiogenic disease in a host with an angiogenic disease, comprising contacting said host with a cephalotaxine in amount sufficient to inhibit angiogenesis, wherein said angiogenic disease is not a solid tumor." The references fail to teach all limitations of claim 1. The Examiner argues that Powell teaches a "method of treating mice for remission of leukemic tumors . . . which comprises administering . . . an effective amount [of] an active compound selected from harringtonine and isoharringtonine." See Office Action page 13. However, as acknowledged by the Examiner, Powell fails to teach the angiogenesis inhibition requirement of claim 1. *Id.* In addition, Powell's experimental model tests the effect of compounds on leukemic tumor cells via "intraperitoneal injections of harringtonine or isoharringtonine." Col. 2 lines 14-16. As such, both the tumor cells and the compound are located in the intraperitoneal cavity of the test animals. As further discussed herein, angiogenesis is not associated with tumor cells in such an environment.

Also, the Examiner argues that "D'Amato teaches that 'angiogenesis has been associated with blood-born tumors, such . . . [as] leukemias . . .' (col. 3, lines 23-31)." See Office Action page 14. D'Amato is directed to thalidomide compounds and thus fails to teach the "cephalotaxine" requirement of claim 1. Further, the Examiner argues that Kawai "teach[es] 'leukemic cell lines . . . [are] representative of non-solid tumor[s]' (see, for example, the abstract at page 201, line 6)." See *id.* However, Kawai fails to teach the "cephalotaxine" requirement of claim 1. Thus, the references fail to teach every limitation of claim 1 and those claims depending therefrom.

2. There is no motivation or suggestion to modify the references to make the presently claimed invention.

The references do not provide the motivation or a suggestion to modify the disclosures taught therein to reach the present invention. As previously discussed, Powell fails to teach all the limitations of claim 1. The Examiner attempts to cure the defects of Powell with D'Amato and Kawai, as discussed above. In particular, the Examiner asserts that the "skilled artisan would have appreciated the leukemia of Powell et al. to be a non-solid tumor and also be considered an angiogenic disease, thus meeting the requirements of the present claims." See page 14 of the Office Action.

The Applicant respectfully disagrees. For the following reasons, a person of ordinary skill in the art would not be motivated to combine the references to make the present invention. Powell discloses testing for the "remission of L1210 and P388 leukemic tumors in mice, . . . accomplished by intraperitoneal injections of harringtonine or isoharringtonine." Col. 2 lines 14-16. The P388 and L1210 strains are well established leukemia models. See In Vivo Cancer

Models, 1976-1982, NIH Publication No. 84-2635 February 1984 (See attached copy). The use of both models includes preparing a quantity of ascitic fluid containing leukemic cells and injecting it intraperitoneally into test animals. As described in the reference, mice are "implanted with the leukemic strains P388 and L1210" (Col. 1 lines 40-41) and then injected intraperitoneally with harringtonine and isoharringtonine in order to assess remission of the leukemic tumors. See Col. 2 lines 14-17 Therefore, in Powell, the leukemic cells reside in the intraperitoneal cavity following the initial implantation.

D'Amato discloses that "angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow . . . [and] plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors" (Col. 3 lines 23-31). As the P388 and L1210 strains in Powell are implanted intraperitoneally, tumor cells are not present in the blood or bone marrow. It follows that the reference does not disclose the treatment of blood born- or bone marrow-associated leukemia. Accordingly, a person of ordinary skill in the art would not be motivated to modify the references' teachings to reach the present invention.

In addition, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. See Col. 6 lines 54-56 and claim 1. The reference provides no suggestion or motivation to modify its teachings to use a cephalotaxine as required by the claims. Similarly, Kawai provides no suggestion or motivation to modify the Powell and D'Amato references to reach the present invention. Thus, the references fail to provide the motivation or a suggestion to reach the presently claimed invention.

3. There is no reasonable expectation of success.

Applicant respectfully asserts that the references do not provide a reasonable expectation of success. As discussed above, Powell's method requires implanting tumor cells in the intraperitoneal cavity of mice and injecting harringtonine or isoharringtonine. In addition, according to D'Amato, angiogenesis is involved in blood born and bone marrow leukemias. Therefore, there is no reasonable expectation that modifying the method of Powell to inhibit angiogenesis would succeed.

As such, the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). The Applicant respectfully requests the withdrawal of this rejection.

B. Chinery in view of D'Amato, Cecil's, O'Dwyer, and Medford

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chinery et al. U.S. Application No. 2001/0049349 ("Chinery") in view of D'Amato et al. U.S. Patent No. 5,712,291 ("D'Amato"), Cecil's Textbook of Medicine, pp. 1060-1074 ("Cecil's"), O'Dwyer et al., *J. Clin. Oncol.*, 4:10(October), 1986, pp. 1563-1568 ("O'Dwyer") and Medford et al. U.S. Patent No. 5,380,747 ("Medford").

1. The references fail to teach every limitation of claim 1 and those depending therefrom.

As currently amended, claim 1 recites a "method of treating an angiogenic disease in a host comprising contacting said host with a cephalotaxine in amount sufficient to inhibit angiogenesis, wherein said angiogenic disease is not a solid tumor." As acknowledged by the Examiner, Chinery fails to teach the angiogenesis inhibition requirement of claim 1. See page 16 of the Office Action. As discussed above, D'Amato fails to teach the "cephalotaxine"

requirement of the present invention. In addition, Cecil's, Medford, and O'Dwyer each fail to disclose the angiogenesis inhibition requirement of claim 1. Thus, the references fail to teach all limitations of the claims.

2. There is no motivation or suggestion to modify the references to make the presently claimed invention.

The Examiner argues that Chinery teaches "a method for the treatment of abnormal cell hyperproliferative conditions which comprise administering to a host . . . an antioxidant . . . and an antineoplastic agent, such as homoharringtonine." See page 15 of the Office Action. However, as previously discussed, Chinery fails to teach the angiogenesis inhibition requirement. The Examiner attempts to cure the defects of Chinery with D'Amato by arguing that "D'Amato provides teachings that would have led one of ordinary skill in the art to appreciate that rheumatoid arthritis, leukemia and blood-born tumors in general, and atherosclerosis are angiogenic diseases." *Id.* at page 17. However, as discussed above, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. The reference provides no suggestion to a person of ordinary skill to modify its teachings to contact a "host with a cephalotaxine" as required by the claims.

In addition, the Examiner asserts

> One of ordinary skill in the art would have been motivated to select homoharringtonine from the listing of antineoplastic agents disclosed by Chinery et al. at page 12 paragraph [152] because homoharringtonine was known to be effective against leukemias and lymphoma (See O'Dwyer et al., see first paragraph on page 1563 and the paragraph bridging pages 1563-4, especially the middle of that paragraph on page 1564, "In vitro testing of [homoharringtonine] against ten human leukemia or lymphoma lines showed a 70-fold difference in growth inhibition between the most sensitive and the most resistant cell lines[)].
>
> Page 18 of the Office Action

The Applicant respectfully disagrees. Neither Chinery nor O'Dwyer disclose the angiogenesis inhibition requirement of the claims. As such, neither reference provides any suggestion to modify its method to reach the present invention with this requirement. The Examiner attempts to cure the defects of Chinery and O'Dwyer through D'Amato. However, as discussed above, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. It contains no suggestion or motivation to modify its teachings to contact a "host with a cephalotaxine" as required by the claims.

> As to non-cancerous conditions such as rheumatoid arthritis, the Examiner argues
>
> [I]t appears that the invention of Chinery et al. is to treat any of such diseases with any of the listed antineoplastic agents [and] because homoharringtonine is identified as an antineoplastic agent, . . . one of ordinary skill in the art would have been motivated to use . . . homoharringtonine for the treatment of rheumatoid arthritis." *Id.*

The Applicant respectfully disagrees. Chinery does not disclose the angiogenesis inhibition or "cephalotaxine" requirement of the claims. As such, it lacks a suggestion or the motivation on at least two counts. First, there is no suggestion to "inhibit angiogenesis" as required by the claims. Second, there is no suggestion or motivation to select homoharringtonine from the listing of antineoplastic agents disclosed by the reference at page 12 paragraph [0152] to treat rheumatoid arthritis as recited for example in claim 3. The Examiner again attempts to cure the defects of Chinery through D'Amato. However, as discussed above, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. It contains no suggestion or motivation to modify its teachings to contact a "host with a cephalotaxine" as required by the claims.

> As to non-cancerous conditions such as inflammatory diseases, the Examiner asserts
>
> One of ordinary skill in the art would have recognized rheumatoid arthritis from the express teaching of Chinery et al. of 'the chronically inflamed state of rheumatoid arthritis" (col. 2, lines 43-44). Also, atherosclerosis would have been

> encompassed by present claim 2 because it was known as an inflammatory disease, (as well as an angiogenic disease as discussed above).
>
> Pages 18-19 of the Office Action. *Id.*

The Applicant respectfully disagrees. As previously discussed, Chinery fails to disclose the angiogenesis inhibition or "cephalotaxine" requirement of the claims. As such, it lacks a suggestion or the motivation on at least two counts. First, there is no suggestion to "inhibit angiogenesis" as required by the claims. Second, there is no suggestion or motivation to select homoharringtonine from the listing of antineoplastic agents disclosed by the reference at page 12 paragraph [0152] to treat inflammatory diseases as recited for example in claim 2. It appears the Examiner again attempts to cure the defects of Chinery through D'Amato. However, as discussed above, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. It contains no suggestion or motivation to modify its teachings to contact a "host with a cephalotaxine" as required by the claims.

As discussed above, the other references cited by the Examiner, Cecil's and Medford, both fail to disclose the angiogenesis inhibition requirement of the claims. Thus, they do not provide the motivation or a suggestion to a person of skill in the art to modify their teachings to reach the present invention.

3. There is no reasonable expectation of success.

Applicant respectfully asserts that the references do not provide a reasonable expectation of success. As discussed above, none of Chinery, O'Dwyer, Cecil's, and Medford disclose the angiogenesis inhibition requirement of the present invention. In addition, D'Amato's method requires the use of a thalidomide compound to treat undesired angiogenesis. It does not disclose

the "cephalotaxine" requirement Thus, there is no reasonable expectation that modifying D'Amato to reach the present invention will be successful.

The Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). The Applicant respectfully requests the withdrawal of this rejection.

Double Patenting Rejections

Claims 1-6 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 15-17 of U.S.S.N. 10/617,927. On January 17, 2006, in response to a Restriction Requirement, Applicant elected claims 19-24. Claims 15-17 stand withdrawn. Therefore, Applicant respectfully requests withdrawal of this rejection, and allowance of Claims 1-6.

In addition, claims 1-6 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 16-21 of U.S.S.N. 10/769,638 or claims 15-20 of U.S.S.N. 10/631,106. Applicants respectfully request that this rejection be held in abeyance until subject matter is allowed in this or other pending applications.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

Dated: Feb. 10, 2006 By: J. P. Bernhardt

Jeffery P. Bernhardt, Reg. No. 54,997 for
Richard F. Trecartin, Reg. No. 31,801

Customer No.: 32940
555 California Street, Suite 1000
San Francisco, CA 94104-1513
Telephone: (415) 781-1989
Facsimile: (415) 398-3249